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• COMMENTARY •

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MicroRNAs: the novel targets for Ebola drugs

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The re-emergence of Ebola viral disease (EVD) in West Africa has caused an international alarm, even panic. As of August 27th, 2014, the Ebola virus (EBOV) has infected 3069 people with 1552 death cases starting from December 2013 (http://www.who.int/csr/don/2014_08_28_ebola/en/). Recently, an outbreak of Ebola hemorrhagic fever in the north of Congo (Democratic Republic) has been confirmed besides Guinea, Liberia, Sierra Leone and Nigeria. So far the epidemic has not been effectively controlled.

Vascular endothelial cell permeability mainly contributes to the hemorrhagic fever during EBOV infection and the consequent high mortality. However, the complete mechanism leading to changes in vascular endothelial cell permeability have not been elucidated. Several factors, including the release of inflammatory mediators, virus directed attacking of endothelium, the release of endosomal cathepsins and the expression of virus-envelope glycoprotein GP, are proposed to be responsible for virus-induced cell injury and the vascular permeability [1]. GP is considered as a viral determinant of EBOV pathogenicity and likely contributes to hemorrhage during infection, as several groups reported that overexpression of GP can induce cell detachment and rounding *in vitro* and *ex vivo* [2]. Similar results were also confirmed by Prof. Jiang and her colleagues [3].

In the article published in this issue, Sheng et al. [3] attempted to explore the molecule mechanism by which GP induces cell damage from a new angle. They evaluated the microRNA levels, using the RNA-Seq method, in human umbilical endothelial cells (HUVECs) that overexpress EBOV GP. At least 18 microRNAs were differentially expressed with high significance in the GP-expressing cells compared to in the GP-negative cells. To investigate the role of those microRNAs in EBOV pathogenesis, the authors knocked down the candidate microRNAs in the GP-expressing cells with microRNA inhibitors. Three microRNA inhibitors, hsa-miR-1246, hsa-miR-320a and hsa-miR-196b-5p, were found to effectively ameliorate the GP-induced cell detachment and rounding. To the best of our knowledge, this is the first time that solid evidence is presented to show that microRNAs are involved in the GP-mediated cell damage.

MicroRNAs are oligo-nucleotides of approximate 21–23 bp in size. These single-stranded noncoding RNA molecules have been identified as one of the most important gene-expression regulators in various physiological processes. In general, they silence the expression of their target genes via degradation of the mRNA or by translational repression. In the paper of Sheng et al. [3], the target genes of hsa-miR-1246, hsa-miR-320a and hsa-miR-196b-5p were predicted using the miRDB database. They further analyzed the expression levels of those genes in the GP-expressing cells by Western blotting and found that seven out of 21 predicted genes were down-regulated comparing with the negative controls. One of the main attractions of their results is that the microRNA inhibitor treatment of HUVECs could result in an increased expression of TFPI (tissue fac-

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tor pathway inhibitor), DAG1 (dystrophin-associated glycoprotein 1) and CFLAR (CASP8 and FADD-like apoptosis regulator). All the three proteins have been previously shown to be associated with cell adhesion and cell survival. TFPI is the primary factor inhibiting the initiation of blood coagulation and can modulate the severity of a wide variety of bleeding and clotting disorders. DAG1 is involved in a number of processes including laminin and basement membrane assembly, cell survival, cell migration, and epithelial polarization. CFLAR is a key anti-apoptotic regulator that inhibits cell death mediated by the death receptors Fas, DR4, DR5, and TNF-R1. Therefore, it is reasonable to infer that hsa-miR-1246, hsa-miR-320a and hsa-miR-196b-5p were involved in Ebola GP-mediated cellular damage through down-regulating the target proteins of TFPI, DAG1 and CFLAR. Their further studies showed that the GP-mediated cytotoxicity could be rescued when microRNA inhibitors or the target-gene (TFPI, DAG1and CFLAR) expression plasmids were transfected into HUVECs or 293T cells that overexpress EBOV GP. Jiang's results developed a new scientific niche for studies on the GP-mediated cytotoxicity and the EBOV pathogenic signaling pathways, and provided a new target for EBOV drug development.

So far, Ebola inhibitors/drugs and vaccines still stuck in laboratories [4]. There are no approved drugs for treatment of Ebola patients or vaccines to protect the people of high exposure risks from Ebola infection. Under the pressure of the urgent circumstances in West Africa, World Health Organization (WHO) committee suggested, upon the patients' informed consent, to use unproven drugs (e.g., Zmapp) and vaccines to control the pandemic. Studies from Jiang's group indicated that inhibitors of hsa-miR-1246, hsa-miR-320a and hsa-miR-196b-5p can alleviate GP-induced cell cytotoxicity and can be served as potential drugs.

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